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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,669	04/09/2004	M. Zouhair Atassi	17525 (AP)	9880

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 05/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/821,669	ATASSI, M. ZOUHAIR	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/2/06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61,63,67-79,81-83,93,94,96-121 and 123-133* is/are pending in the application.

4a) Of the above claim(s) *18-30,44-53,74-79,81-83 and 102-113* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,31-43,54-61,63,67-73,93[illegible],114-121 and 123-133* is/are rejected.

94-101

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *See Continuation Sheet* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims subject to restriction and/or election requirement are 1-61,63,67-79,81-83,93,94,96-121 and 123-133.

DETAILED ACTION

Claims 1-61, 63, 67-79, 81-83, 93-94, 96-121, 123-133 are pending.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

1. Newly submitted claims 18-30, 44-47, 48-53, 74-79,81-83, 102-113 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

2. Claims 18-30, 74-79, 81-83,102-113 have been amended to be directed to a different method/process, wherein the tolerigizing agent is conjugated to one or more botulinum toxin peptides, and the previously examined methods were directed to mixtures of two or more botulinum toxin peptides together with a tolerigizing agent. The instantly amended, claimed inventions are directed to independent and distinct species of invention not previously examined in the first action.

3. Claims 44-47 previously ~~was~~ were directed to an in vitro method for removing botulinum toxin blocking antibodies from a blood sample, but ~~has~~ have been amended to be a combination method of in vitro removing botulinum toxin blocking antibodies, combined with *in vivo* returning the blood sample to the individual. Additionally, the originally presented claims obtained the blood from a patient, but now the blood is being obtained from an individual, the individual not being so claimed in such a was as to have had contact with botulinum toxin. The newly amended combination of claim limitations defines an independent and distinct method/process not previously examined in the first action on the merits.

4. Claims 48-53 were previously directed to method of detecting antibodies to any one of the known full length botulinum toxins, serotypes A-G, but have been amended to be directed to methods of detecting antibodies to peptides fragments rather than antibodies immunoreactive to full length botulinum toxin proteins. The newly amended methods/processes are independent and distinct from the methods previously examined in the first action, in light of the fact that a different combination of reagents are used in the claimed methods.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 18-30, 74-79, 81-83,102-113 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Objections/Rejections Withdrawn

5. ***Claim Objection Withdrawn*** Claims 1-47 objected to for minor informalities for reciteing terms set forth in brackets has been obviated by removal of the bracktets.

6. ***Claim Objection Withdrawn*** Claims 1-47 objected to for reciting Markush groups, set apart by semi-colons and not reciting the correct format A, B, C and D, has been obviated by claim amendment which removes the semi-colons and the additional "and".

7. ***Rejection Withdrawn, Claim Rejections - 35 USC § 112*** Claims 31-43, 84-92,114-122 rejected under 35 U.S.C. 112, first paragraph (Scope, vaccine) has been obviated through cancellation of claims 84-92 and 122, and amendment of the remaining claims to no longer recite the term "vaccine".

8. ***Rejection Withdrawn*** Claims 54-133 rejected under 35 U.S.C. 112, second paragraph for claiming BoNT/A peptides have a length of 60 amino acids, but all of the ranges of amino acids recited in the claims are about 26-27 amino acids in length; has been obviated in light of a reference sequence, SEQ ID NO 1, having been inserted into all of the claims.

9. ***Rejection Withdrawn*** Claims 1-47, 54-133 rejected under 35 U.S.C. 112, second paragraph, for reciting the phrase "conservative variant" has been obviated in light of the amendment of the claims to define the variant to be a conservative variant defined in the instant Specification, the variantions being introduced into SEQ ID NO 1.

1. ***Rejection Withdrawn Claim Rejections - 35 USC § 102*** Claims 1-4, 14,16-17,31-34,54,56-60,63-70,72,73,84-91,93-99,114-120,123,125-129,132 rejected under 35

U.S.C. 102(b) as being anticipated by Rosenberg et al (1996), in light of the amendment of the claims to no longer read on the disclosed peptides of Rosenberg et al.

2. ***Rejection Withdrawn Claim Rejections - 35 USC § 102*** Claims 18-30 rejected under 35 U.S.C. 102(e) as being anticipated by Allison (US 2002/0197278 A1, December 26, 2002), in light of the claims having been amended to be directed to an independent and distinct invention, which has been withdrawn herein; election by original presentation.

3. ***Rejection Withdrawn Claim Rejections - 35 USC § 102*** Claims 31-34 rejected under 35 U.S.C. 102(b) as being anticipated by Oshima et al (1998) in light of the amendment of the claims to require a peptide that comprises 785-803 to be administers to an individual.

4. ***Rejection Withdrawn Claim Rejections - 35 USC § 102*** Claims 44 is rejected under 35 U.S.C. 102(b) as being anticipated by Oshima et al (1997). in light of the claims having been amended to be directed to an independent and distinct invention, which has been withdrawn herein; election by original presentation.

5. ***Rejection Withdrawn Claim Rejections - 35 USC § 102*** Claims 44-47 rejected under 35 U.S.C. 102(b) as being anticipated by Singh et al (1997) in light of the claims having been amended to be directed to an independent and distinct invention, which has been withdrawn herein; election by original presentation.

6. ***Rejection Withdrawn Claim Rejections - 35 USC § 102*** Claims 48-50 and 52-53 rejected under 35 U.S.C. 102(b) as being anticipated by Naumann et al (1998), in light of the claims having been amended to be directed to an independent and distinct invention, which has been withdrawn herein; election by original presentation.

7. ***Rejection Withdrawn Claim Rejections - 35 USC § 102*** Claims 48 and 51 rejected under 35 U.S.C. 102(b) as being anticipated by Oshima et al (1998), in light of the claims having been amended to be directed to an independent and distinct invention, which has been withdrawn herein; election by original presentation.

8. ***Rejection Withdrawn Claim Rejections - 35 USC § 102***Claims 84,86-87, 88-94, 95-100, 114, 116-121,123,125-130,132 are rejected under 35 U.S.C. 102(b) as being anticipated by Bavari et al (1998), in light of the amendment deleting the peptide disclosed by Bavari et al.

9. ***Claim Rejections - 35 USC § 103***Claims 74-83 and 102-111 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allison (US 2002/0197278 A1, December 26, 2002) in view of Oshima et al. in light of the claims having been amended to be directed to an independent and distinct invention, which has been withdrawn herein; election by original presentation.

10. ***Claim Rejections - 35 USC § 103*** Claims 102 and 112-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allison (US 2002/0197278 A1, December 26, 2002), in view of Atassi et al (US Pat. 6,048,529). in light of the claims having been amended to be directed to an independent and distinct invention, which has been withdrawn herein; election by original presentation.

11. ***Claim Rejections - 35 USC § 103*** Claim 71 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenberg et al in view of Dertzbaugh et al. in light of the amendment of the claims to no longer read on the disclosed peptides of Rosenberg et al.

12. ***Claim Rejections - 35 USC § 103*** Claims 123 and 133 are rejected under 35 U.S.C. 103(a) as being obvious over Kubota et al (1997) in view of Harlow (1988, reference cited in Applicant's specification), is herein withdrawn in light of Applicant's traversal and amendments to the claims.

Response to Arguments

13. Applicant's arguments filed March 2, 2006 have been fully considered but they are not persuasive.

1. ***Rejection Maintained Claim Rejections - 35 USC § 102*** Amended claims 1-13, 15,17,31-43, 54-61, 114-121,123-132 rejected under 35 U.S.C. 102(b) as being anticipated by Dertzbaugh et al (1996) is traversed on the grounds that the instant Specification defines the recited peptides to be "no more than 60 amino acids in length".

2. While the examiner agrees that one of the definitions provided by the instant Specification is directed to peptides of no more than 60 amino acids in length, the instant Specification also defines the term "peptide" with the definition "peptide" means two or more amino acids covalently bonded together." (see Definition at [062], page 18, lines 1-2) .

3. Additionally, claim 54 requires the antibodies to bind to peptides that comprising 60 amino acids in length, and would functionally bind to peptides of between 1-10 amino acids that make up the epitope to which they bind. The method of claim 54 defines the antibodies as having the functional requirement to bind to peptides that are 60 or less amino acids in length, but are not required to be contacted with peptides with an upper limit size of 60 amino acids. In light of the combination of claim limitations set forth in the amended claims that defines the antibody binding characteristics and not the peptide to which the antibodies are immunoreacted the prior art rejection is being maintained.

4. The methods step of "determining" of claim 54 (and all claims that depend there from) determines the presence or absence of antibodies with a specific functional reactivity, but how they are determined is not limited to any specific immunoassay format, nor limited to only

reacting with peptides with 60 amino acids or less. No peptides are provided in the method of claim 54; only determining the presence of antibodies is required by the claimed method(s).

5. Therefore Applicant's traversal is directed to a species of invention disclosed in the instant Specification, but Not claimed. The peptides of the claims may comprise two amino acids (definition in Specification page 18), specifically 6 consecutive amino acids of SEQ ID NO 1 and the antibodies must be able to immunoreact with a peptide that is not more than 60 amino acids in length or comprise 6 consecutive amino acids of the recited ranges of amino acids.

6. Dertzbaugh et al discloses BoNT/A peptides that comprises at least 6 consecutive amino acids of the peptides 785-803 and 1275-1296. The disclosedpeptides 630-808 and 780-939, both comprise the amino acid sequence range of 785-803.) and the disclosed peptide of 1150-1289 comprises 15 consecutive amino acids of the range 1275-1296.

7. The peptides and disclosure of Dertzbaugh et al still anticipate the instantly claimed invention in amended claims 1-13, 15,17,31-43, 54-61, 114-121,123-132.

New Claim Limitations/New Grounds of Rejection

Claim Rejections - 35 USC § 102

8. Claims 93-94, 96, 98 are rejected under 35 U.S.C. 102(b, copy write 2002) as being anticipated by Atassi (Chapter 38, pages 385-407).

Atassi disclose the instantly claimed invention directed to peptide that comprises 6 consecutive amino acids of the range 659-677 of SEQ ID NO 1, wherein the peptide was less than 30 amino acids in length, and consisted of residues 663, 664, 665, 666, 667 and 668 (6 consecutive amino acids, see page 385, col. 2, near bottom of first paragraph). This peptide

anticipates the newly amended claims.

9. Claims 93-94, 96, 98 are rejected under 35 U.S.C. 102(b) as being anticipated by Oblatt-Montal et al (1995).

Montal et al disclose the instantly claimed invention directed to peptide that comprises 6 consecutive amino acids of the range 659-677 of SEQ ID NO 1, wherein the peptide was less than 30 amino acids in length, and conprised residues 659-681 (see page 1491, col. 1, paragraph 3). This peptide anticipates the newly amended claims.

10. Claims 93 and 96 are rejected under 35 U.S.C. 102(b) as being anticipated by Sesardic et al (WO94/21684).

11. Sesardic et al (WO94/21684) disclose the instantly claimed invention directed to peptide that comprises an amino acid sequence of SEQ ID NO 1, range 827-845, is not a variant but comprises an amino acid sequence of one of the recited peptides and is not more than 30 amino acid in length, wherein the peptide comprised amino acids 841, 842, 843, 844, 845 of Botulinum toxin type A, (see page 12, Table 1, H chain, peptide "P3", and contained 15 amino acids). This peptide anticipates the newly amended claims.

12. Claims 93 is rejected under 35 U.S.C. 102(b) as being anticipated by Raju et al (1996).

13. Raju et al disclose the instantly claimed invention directed to peptide that comprises an amino acid sequence of SEQ ID NO 1, range amino acids 634-642, wherein the peptide of Raju et al is referred to as H176-195 and shown in Figure 1, on page 81 and shares 100% sequence

identity with SEQ Id No 1 over 9 consecutive amino acids and stimulated an immune response (see Figure 3, Frame 2, page 83). The disclosed peptide comprises an amino acid sequence of one of the recited peptides and is not more than 30 amino acid in length, wherein the peptide comprised amino acids 568-577 of Botulinum toxin type A. This peptide anticipates the newly amended claims.

Claim Rejections - 35 USC § 103

14. Claims 1-16, 55-61,63, 67-73, 93-94,96-101, 114-112, 123-133 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dertzbaugh et al (1996) in view of Bavari et al (effective filing date 1998).

15. Dertzbaugh et al teach and show Clostridium botulinum neurotoxin peptides (see page 1540, Figure 1, top of col. 1; page 1539, col. 1-2 and page 1541, Tables 1-2) that upon administration to a mammal together with an adjuvant (see page 1542, col. 1, paragraph 3) induce a protective immune response (see page 1539, col. 2, paragraph 2) which was found to cross reactive with other botulinum serotypes (E and D, see page 1541, col. 1, last paragraph) by ELISA or immunoblot (see page 1541, col. 1, paragraph 2). Dertzbaugh et al differs from the instantly claimed invention by failing to show the peptides to be of a size less than or equal to 60 or 40 amino acids in length.

Bavari et al teach and show means and methods of producing of overlapping peptides of 25 amino acids (see [0004])in length for epitope mapping botulinum toxins in an analogous art for the purpose of developing shorter, more readily expressed antigens for future vaccine development ([0031]),

as well as teach the production of neutralizing polyclonal [0005; 0025] and "monoclonal antibodies [0004, top of paragraph; 0038 "Harlow"]" in an individual (mammal) administered (see [0023]) synthetic (see[0059, "recombinant"]) dominant neutralizing epitiope (see [0004, page 1, last few sentences]) peptide fragment (see[0030]) obtained from botulinum toxin A toxin (see [0021]) together with an adjuvant [0080] and methods of determining the presence or absence of neutralizing antibodies, that include IgG antibodies ([0067]) in a biological sample ([0044]) by enzyme-linked or radioimmuno- assay labeling (see [0043]) .

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the peptides of Dertzbaugh et al to be peptides of less than 60 or 40 amino acids in length as taught by Bavari et al because both Dertzbaugh et al and Bavari et al are directed to identifying protective epitopes presented by Clostridum botulinum neurotoxin for vaccine development and Bavari et al teach the advantage of shorter, more readily expressed peptide immunogens that about 25 amino acids in length as they are readily used for determining the presence of or the induction of neutralizing polyclonal and/or monoclonal antibodies because the peptides can be expressed recombinantly

In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining peptides of less than 60 or 40 amino acids as taught by Bavari et al obtained from the L-chain, N- and C-terminals of the H-chain of botulinum toxin A as taught by Dertzbaugh et al, for administration to a mammal for induction of an immune response, as well as utilization of the peptides for determination of antibodies in an individual because Dertzbaugh et al successfully identified peptides that comprised immunogenic epitopes that induced a protective immune response when

administered to a mammal, wherein the antibodies induced/produced by the peptides were determined by immunoassay and Bavari et al teach and show the successful utilization that shorter antigens of 25 amino acids for induction of neutralizing monoclonal antibodies (to the peptides which provide a basis for predicting epitopes and neutrailizing antibodies directed against botulinum neurotoxin, one of the most potent toxins known to man (see Dertzbaugh et al, page 1538, col. 1, first sentence).

Conclusion

16. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

17. Lacy et al (1999) is cited to show sequence homology between Clostridium botulinum neurotoxin serotypes.

18. Lebeda et al (1997) is cited to show the induction of neutralizing monoclonal antibodies to a 25 mer peptide of Botulinum toxin A (see last page).

19. Byrne et al (2000) is cited for teaching advantages of recombinant vaccines that comprise fragments, to include 19 mers (see page 957, section 3., col. 2, paragraph 4)of botulinum neurotoxin wherein the recombinant products would be purer, well characterized with respect to identity, efficacy, potency, consistency, stability (see page 964, col. 1, middle of first paragraph), less reactogenic and overall safety. Additionally, the well characterized products would be produced at a lower cost, and higher production level resulting in reduced cost of vaccine products (see page 957, col. 1, paragraph 2).

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
May 1, 2006

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